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Association of Thyroid Hormones with Oxidative Stress Markers in Patient with Hyperthyroidism

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Abstract

Background: Biomarkers for diagnosing the occurrence and development of hyperthyroidism constitute a major worldwide clinical scrutiny. Evidence is continuing in an investigation about the most relevant biomarkers in developing the disease.

Objective: To discover and correlate the most dependent biomarkers in developing hyperthyroidism in both genders.

Patients and Methods: In the present study, two groups were included, the first group: forty males and females with chronic hyperthyroidism were enrolled. Serum levels of thyroid hormones, lipid profile, oxidative stress marker, blood glucose, and renal function markers were measured and compared with euthyroid subjects.

Results: The present study revealed that referral biomarkers were varied between genders with a remarkable association of hyperthyroidism with serum cholesterol, triglycerides, and low-density lipoproteins in females, while nitrites and creatinine and MDA were significantly correlated in male patients.

Conclusion: In this study, we found that indicating biomarkers for hyperthyroidism could be differentially changed in different genders that help in understanding the progression and development of the disease.

Keywords: Hyperthyroidism, oxidative stress, malondialdehyde, creatinine, nitrite.

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Introduction

Oxidative stress, representing extreme levels of free radicals in some chronic diseases, including hyperthyroidism, has been correlated with laboratory tests including lipid indices, hematological values, oxidative stress agents, and endogenous antioxidant potentials [1]. However, after years of clinical and experimental assessments of relevant biomarkers' implications in developing hyperthyroidism, the most reliable strategy for accurately identifying the most relevant biomarkers in the disease is still poorly investigated. Hyperthyroidism, like any other hormonal disturbances, if not the most, gives rise to disturbing physiological relevant parameters in both extremities [2,3] that predicted specifying the disease treatment as a complicated task. Given that hypothyroidism results in dyslipidemia [4] oxidative stress [1], and in more severity, to mental stress [5], insulin impairment[6] that uncover the

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importance of the question; which laboratory parameters should be taken into consideration targeted to modulate the disease progression and development?. Recently, data analysis and applied distinctive statistical concepts in medical researches highlighted the dominant influence of some variables to have the key impact on the progress and development of diseases [7]. The current study aimed to find out which variable is more correlated with the progression of hyperthyroidism in both genders.

Patients and Methods

Subjects and study design

In this case control study, two groups were included: the first group: forty healthy persons (male and female), in whom the levels of thyroid-stimulating hormones (TSH), T3, and T4 were fallen in physiological boundaries in ages between 20 and 75 years. The second group: forty patients with hyperthyroid disease, elevated levels of T3 and T4 with a decreased level of TSH with the ages between 19 and 76 years with symptoms of hyperthyroidism like (sweating, palpitation, polyuria, increased appetite) were enrolled.

Inclusion and Exclusion criteria

From careful history taking, physical examination, and routine laboratory tests, thesubject'ss participants were found not to have other diseases or infections. Inclusion criteria were the clear thyroid dysfunction that was characterized by decreased levels of TSH and increased levels of T4 in T3 in fasting blood samples. Lipid profile including high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides and total cholesterol were measured, besides to other biochemical tests such as creatinine, urea, and glucose have also been included. Exclusion criteria involved smoker, pregnancy, cardiac disease, alcoholics, diabetes. The blood sample was collected in the surgical specialty hospital cardiac center from the period of March 2021 to June 2021.

After the blood was taken by the laboratory staff of the hospital from the subjects, blood samples were allowed to clot at room temperature then serum was separated by centrifugation and transferred into Eppendorf tube 1.5 ml by disposable pipette preserved of serum and stored at -52 C until the samples were processed for biochemical analysis. The serum levels of TSH, T3, and T4 were measured by a fully automated immune analyzer (Cobas e C411Roche diagnostics, HITACHI, Japan). Serum glucose, triglyceride, total cholesterol, HDL, LDL, MDA, nitrite, creatinine, and urea were measured by a fully automated biochemical analyzer (Cobas c311 HITACHI).

Statistical Analysis

Collected data were analyzed for normality tests. Statistical test power was set to 80% and alpha at 5%. When the data passed the normality tests, data were expressed as means ± standard error of means (SEM). One-way analysis of variance (ANOVA) and Sidak comparison test was were used.The association between thyroid hormones with other independent variables was done by Pearson coefficient of correlation using IBM-SPSS statistical software version 25. The null hypothesis was rejected when the alpha was less than 0.05. For the quantitative measures accuracy, the area under the receiver operating characteristic (ROC) curve (AUROCC) which was derived by plotting the predicted probability against the actual

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positive state. An AUROCC of 1.0 indicates the perfect discrimination accuracy between diseased and non-diseased subjects; an AUROCC of 0.5 means the disability of diseased discrimination.

Results

In the studied populations, the alteration in T3, T4, and TSH were as follow: the serum T3 and T4 were elevated remarkably in both male and female patient groups, as can be seen in Figure (1) and Table (1), compared to euthyroid subjects, with highly significant damping in TSH (p=0.0001) in both patient groups. Considering biochemical relevant tests in hyperthyroidism and euthyroid subjects during the study, Table (1) shows that serum MDA in males was increased significantly (5.334±0.826, p=0.018) with non-significant change in female groups, the result that seemed to cover the general impacts of the same parameter in the whole subjects. Nitrite was only elevated significantly in female patients (control;19.80 ± 3.312, female patients; 34.01 ± 5.681, p=0.042), compared with euthyroid subjects. In this study, as observed in Table (1), some clinical tests did not change significantly in all groups, (glucose, HDL, and urea), while male patients, cholesterol was decreased in (136.4 ± 15.27 mg/dl) as compared to euthyroid states (174.7 ± 7.946 mg/dl), P= 0.0412, and LDL values were decreased (75.00 ± 10.98, P=0.043) as compared to control group (111.2 ± 7.343), and a decrease in TG (103.3 ± 15.95, P=0.0253) as compared to control subjects (211.8 ± 21.00) with no changes in female groups. However, creatinine was increased significantly in both male and female groups (0.966 ± 0.033, 0.722 ± 0.031), respectively. In this study, the AUC was used for sensitivity and specificity test, as shown in Figure (2), to find out the sensitivity in predicting or detecting the cut-off values for early diagnosing the progression and development of hyperthyroidism. The analyzed data in Table (2) showed that in males each of cholesterol, TG, Nitrite, MDA, LDL Glucose, creatinine were exceeded %70 of the under curve area, with more particularly, cholesterol, TG, and LDL that exhibited remarkable significant values.

While in females, the vast majority of the clinical tests (except nitrite and creatinine) did not approach the acceptant levels of sensitivity, the result, which in turn, will affect and discriminate the cut-off values from both sexes. Furthermore, in Table (3), the applied Pearson correlation revealed that some parameters, might preferentially, correlate with a particular thyroid hormone imbalance. In males, cholesterol (0.482), TG (0.38), and LDL (0.546) seemed to be positively correlated with T3 with taking into consideration that the rest of the parameters were either weakly or non-significantly correlated in both extremities. In females, nitrite strongly and positively correlated with T4, MDA with T3, and creatinine with TSH, (0.989, 0.814, 0.958), respectively. This correlation between diagnosing tests and hyperthyroidism development and progression will provide helpful therapeutic strategies that could individualize the most relevant parameters in different genders.

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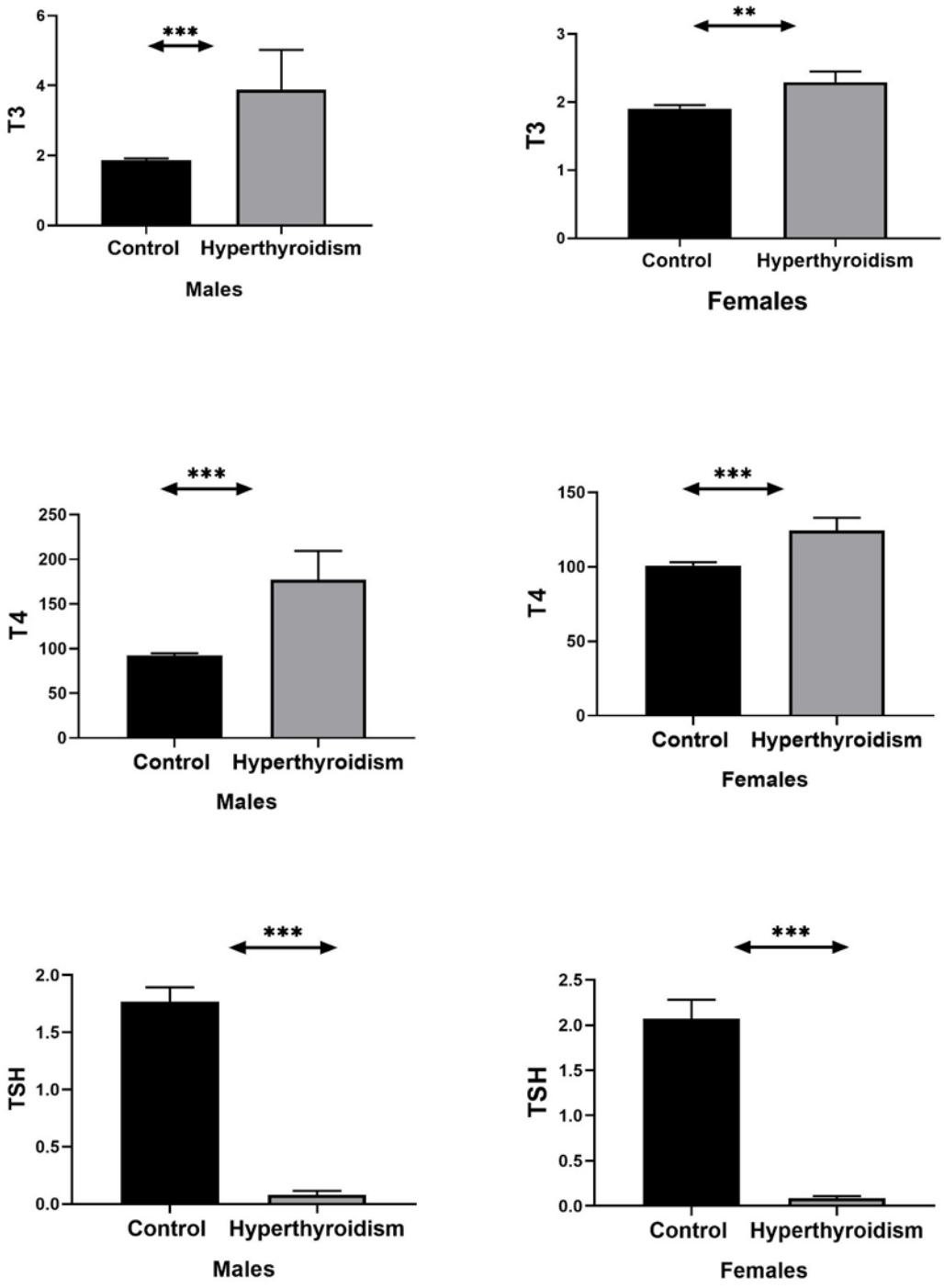

Figure (1): Thyroid hormones tests in both males and females with hyperthyroidism compared to euthyroid subjects.

** represents statistical difference at p<0.01.
*** represents statistical differences ap<0.001

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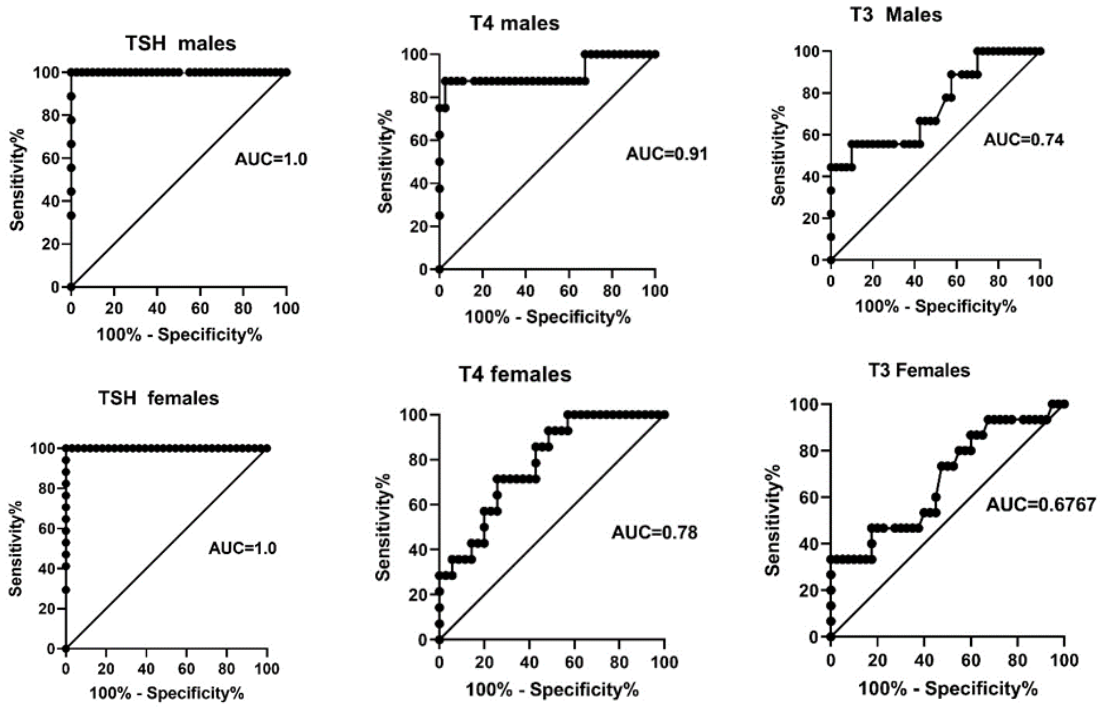

Figure (2): Sensitivity and specificity test of thyroid hormones in both males and females with hyperthyroidism. The area under the curve (AUC)

Table (1): Thyroid hormones and biochemical tests in both males and females with hyperthyroidism compared to euthyroid subjects

	Males			Females		
	Control	**Patients**	**p-values**	**Control**	**Patients**	**p-values**
T_3	1.868 ±0.049	3.889 ±1.135	0.0004	1.907 ±0.053	2.294 ±0.157	0.0041
T_4	92.40 ±2.241	177.2 ±32.19	0.0001	101.0 ±2.10	124.3±8.598	0.0006
TSH	1.769 ±0.125	0.081±0.0328	0.0001	2.069±0.213	0.086 ±0.022	0.0001
MDA	2.280 ±0.733	5.334 ±0.826	0.018	4.172 ± 1.238	5.771 ±1.006	0.32
Nitrite	38.37 ±10.56	17.19 ±3.115	0.05	19.80 ±3.312	34.01 ± 5.681	0.042
glucose	186.3 ±18.76	124.7±11.69	0.126	145.8± 16.35	97.67±6.888	0.297
cholesterol	174.7±7.946	136.4±15.27	0.0412	164.5±6.225	170.8±14.19	0.718
LDL	111.2±7.343	75.00±10.98	0.043	105.8±5.817	110.8±13.54	0.737
HDL	39.43±1.618	40.29±3.765	0.83	40.78±1.746	40.80±4.306	0.996
TG	211.8±21.00	103.3±15.95	0.0253	164.5±6.925	169.6±38.9	0.8227
creatinine	0.966±0.033	1.194±0.097	0.0216	0.722±0.031	0.565±0.035	0.0156
urea	36.88±3.624	37.17±3.497	0.974	35.26±2.605	34.60±5.980	0.916

* The units of measurement; T_3, T_4, and TSH; (nmol/l), glucose, cholesterol, LDL, HDL, TG, creatinine, and Urea;(mg/dl), MDA and nitrite;(µmol/l).bold values represent statistical significance

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Table (2): Area under the curve of thyroid hormones and biochemical and kidney function tests in both male and female patients with hyperthyroidism

		Male			Female	
	AUC	**SEM**	**P-value**	**AUC**	**SEM**	**P-value**
T3	0.7417	0.09878	0.0247	0.6767	0.08441	0.0452
T4	0.9122	0.07988	0.0003	0.7837	0.06735	0.0021
TSH	1	0.000	0.0001	1.000	0.000	0.000
Cholesterol	0.7595	0.1138	0.0346	0.5556	0.1367	0.6971
TG	0.8312	0.07781	0.0065	0.5556	0.2056	0.6971
Nitrite	0.7286	0.1274	0.1184	0.7917	0.1124	0.0433
MDA	0.8095	0.1118	0.039	0.6889	0.1315	0.1651
LDL	0.7778	0.1093	0.0338	0.5667	0.1425	0.6404
HDL	0.5286	0.1267	0.8132	0.5074	0.1483	0.9586
Glucose	0.7267	0.1062	0.0891	0.7727	0.126	0.1323
Creatinine	0.7735	0.1051	0.0508	0.8095	0.08139	0.014
Blood Urea	0.6319	0.08969	0.3056	0.5522	0.1394	0.7189

Table (3): Correlation between thyroid hormone and oxidative stress markers, lipid profiles, and kidney function tests in male and female patients with hyperthyroidism

Female						
	T3		**T4**		**TSH**	
	r	p-value	r	p-value	r	p-value
Cholesterol	0.482	**0.016**	0.321	0.084	-0.150	0.263
TG	0.380	**0.049**	0.338	0.073	-0.040	0.433
Nitrite	0.264	0.131	-0.298	0.101	0.034	0.443
MDA	-0.227	0.168	-0.026	0.457	-0.012	0.480
LDL	0.546	**0.006**	0.129	0.294	-0.265	0.130
HDL	-0.103	0.332	0.017	0.472	-0.343	0.069
Glucose	-0.297	0.102	-0.048	0.420	-0.111	0.320
Creatinine	0.345	0.068	-0.139	0.280	-0.118	0.310
Blood Urea	0.319	0.085	0.032	0.448	-0.074	0.378
Male						
	r	p-value	r	p-value	r	p-value
Cholesterol	-0.572	0.157	-0.003	0.498	-0.347	0.284
TG	-0.434	0.233	0.552	0.168	0.239	0.349
Nitrite	-0.446	0.226	0.989	0.001	0.219	0.362
MDA	0.814	0.047	-0.142	0.410	0.187	0.381
LDL	-0.404	0.250	-0.126	0.420	-0.475	0.210
HDL	-0.033	0.479	-0.469	0.213	-0.251	0.342
Glucose	-0.560	0.163	0.661	0.112	0.499	0.196
Creatinine	-0.590	0.148	0.502	0.194	0.958	0.005
Blood Urea	0.113	0.428	0.419	0.241	-0.260	0.336

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Discussion

In this study, we were successful to uncover the relation of some biochemical markers to hyperthyroidism were varied between genders. In males, the biomarkers indices representing TG cholesterol, LDL, nitrite, creatinine, and MDA were changed while in females only nitrite and creatinine showed significant changes. These results highlighted that in hyperthyroidism these variables could not figure out the disease impacts on both genders equally that came inconsistent with Zhao, (2011) [8] who found that aged females were more prone to have high lipid indices than males. Additionally, some of these parameters (cholesterol, TG, LDL, and MDA) showed a greater area under the curve that added another dimension to the nature of changes made by hyperthyroidism in males. However, in females, nitrite and creatinine predominantly exhibited significant changes that revealed the explanatory nature of the present study because other studies by Fricker, (2003) [9] and Kumari (2017) [10] who generalized the creatinine elevation in hyperthyroidism and negative correlation between nitrite and thyroid hormones, respectively, without taking the gender factor in consideration.

Moreover, the correlation test outputs revealed other interesting facts that came inversely with our expectations. In females, only T3 hormone showed to have a moderate correlation with cholesterol, TG, and LDL that accurately differentiated the impact of gender on these dependent parameters while previous works by Rizo (2011) [11], Jian (2017), and Alsalmi (2018)[12,13] did not discriminate this effect.

It is worth noting that in males TSH had a strong positive relationship with creatinine and weak negative in females that, again as an impact of gender, could not be observed clearly in other studies that generalized the positive relationship between TSH and creatinine [10, 14, 15].

On the other hand, T4 and T3 hormones were positively correlated with MDA and nitrite, respectively. It is worth noting that no earlier studies [16] [17] [18] [19] nor recently published works [20] [21] were applied the impacts of gender on oxidative stress marker and nitrite levels in hyperthyroidism, but in the current study, these parameters were more likely to coexist with the disease in male than in the female. Furthermore, hyperthyroidism has been reported to be negatively correlated with blood urea in early and recent works [22, 23], but in this study, the significant levels of blood urea alteration in both groups were far off been included within the influenced parameters. Additionally, in the present study, similar results were noticed for glucose and HDL where they did not exhibit significant changes that came inconsistent with other studies that referred to a positive relationship between hyperthyroidism and glucose levels and impairment of insulin signaling [6, 24, 25] and a negative correlation with HDL [26, 27].

Conclusions

This case-control study has argued that the nature of correlation between some hyperthyroid disease biomarkers and dependent hormonal factors might be multifarious that, in turn, will add some modifications in diagnosis and controlling the disease in different genders. Moreover,

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age and many other independent variables play pivotal role in interpretation the real relevant impacts on the disease development.

Recommendations

Explanatory researches need to be done for further confirming the nature of association between thyroid dysfunction and pathophysiological risk predictors in developing the disease.

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Ethical clearance: The study was carried out and ethical clearance was obtained by the medical care committee of the College of Dentistry-Hawler Medical University.

Conflict of interest: Nill

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ارتباط هورمونات الدرقية بدلائل الكبت التاكسدي في مرضى فرط الدرقية

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الملخص

خلفية الدراسة: تشكل المؤشرات الحيوية لتشخيص حدوث وتطور فرط نشاط الغدة الدرقية اجراءات سريرية واسعة الانتشار. بينما تكون هذه الدلائل مستمرة التناول في البحث العلمي حول المؤشرات الحيوية الأكثر صلة بتطور المرض، في حين أن الأدلة المتاحة قد أظهرت ارتباطات كبيرة بين المرض والاختبارات البيوكيميائية ، ومع ذلك ، فإن قوة وطبيعة هذه العلاقات تحتاج إلى مزيد من التوضيح.

اهداف الدراسة: لتمييز قوة وطبيعة الارتباط بين فرط نشاط الغدة الدرقية وبعض المؤشرات الحيوية الكيميائية والكبت التأكسدي في كلا الجنسين.

المرضى والطرائق: في الدراسة الحالية ، تم تضمين مجموعتين ، المجموعة الأولى: تم تسجيل أربعين من الذكور والإناث (تتراوح أعمارهم بين ١٩-٧٦) يعانون من فرط نشاط الغدة الدرقية المزمن. تم قياس مستويات هرمونات الغدة الدرقية ، ونسبة الدهون ، وعلامة الإجهاد التأكسدي ، وجلوكوز الدم ، وعلامات وظائف الكلى في الدم ومقارنتها مع المجموعة الثانية السليمة من أمراض الغدة الدرقية والتي تمثل المجموعة الضابطة (تتراوح أعمارهم بين ٢٠-٧٥).

النتائج: كشفت الدراسة الحالية أن المؤشرات الحيوية كانت متنوعة بين الجنسين مع ارتباط ملحوظ بفرط نشاط الغدة الدرقية مع كوليسترول الدم ، والدهون الثلاثية ، والبروتينات الدهنية منخفضة الكثافة في الإناث ، بينما كان النتريت والكرياتينين و مالون ثنائي الديهايد مرتبطة بشكل كبير في المرضى الذكور.

الاستنتاجات: في هذه الدراسة ، وجدنا أن المؤشرات الحيوية التي تشير إلى فرط نشاط الغدة الدرقية يمكن أن تتغير بشكل تفاضلي في مختلف الأجناس التي تساعد في فهم المرض وتطوره.

الكلمات المفتاحية: ا فرط نشاط الغدة الدرقية ، الإجهاد التأكسدي ، دهون الدم ، هرمونات الغدة الدرقية

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تاريخ قبول البحث: ١٥ شباط ٢٠٢٢

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[٤،٣،٢] كلية العلوم - جامعة صلاح الدين - أربيل - العراق